Carcinoma of unknown primary: Retrospective study about 437 patients treated at Salah Azaiez Institute

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Carcinomes de primitif inconnu: Etude rétrospective à propos de 437 patients traités à l'institut Salah Azaiez

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R É S U M É

Prérequis : Les carcinomes de primitif inconnu (CAPI) sont définis comme des métastases de carcinomes confirmées histologiquement sans primitif décelé au moment de la décision thérapeutique.

But: Décrire les caractéristiques épidémiologiques, anatomocliniques, thérapeutiques et les facteurs pronostic des patients traités à l'institut Salah Azaiez (ISA) pour CAPI.

Méthodes: Nous avons revu les dossiers de 437 cas de CAPI entre 1994 et 2006. Nous avons analysé les aspects épidémiologiques, anatomocliniques, thérapeutiques et nous avons classé les cas en entitées favorable et défavorable. L'analyse statistique a été réalisée par le logiciel R et les courbes de survie ont été faites par la méthode de Kaplan-Meier.

Résultats: 437 patients ont été recensés. L'âge médian était 60 ans. Le sex-ratio était 1,8. Les métastases les plus fréquentes étaient ganglionnaires (56,5%), osseuses (29,7%) et hépatiques (28%). 33% des patients avaient une métastase unique. L'adénocarcinome (50,5%) était le type histologique le plus observé. Les entités favorables représentaient 10,5% des cas. 141 patients ont eu une chimiothérapie(CT), dont 83% à base de cisplatine, avec 13% (58 patients) de réponse objective. 24 parmi les 58 (41%) ont rechuté. La survie médiane était 7 mois. Les facteurs de mauvais pronostic étaient: métastases multiples (p=0,00033), >3 sites atteints (p=0,03), carcinome indifférencié et adénocarcinome (p>0,0001), métastases hépatiques (p=0,0137), osseuses (p=0,00653), surrénaliennes (p=0,0334). Les patients ayant eu une CT (p>0,001) et ceux une CT à base de cisplatine avaient une meilleur survie (p=0,01).

Conclusion: Notre étude rétrospective faite avec le minimum d'explorations confirme la difficulté pour retrouver le primitif.

M o t s - c l é s

Métastases, carcinome, primitif inconnu, survie, pronostique

S U M M A R Y

Background: Carcinoma of unknown primary (CUP) origin is defined as histologically confirmed metastatic carcinoma in the absence of a detectable primary site at the time of making therapeutic decision.

Aim: To report epidemiological, clinical, histopathological, therapeutic, and prognostic features of CUP's patients collected at the Salah Azaiez institute (SAI).

Methods: We reviewed retrospectively the files of 437 CUP-patients in SAI between January 1994 and December 2006. We analyzed their epidemiological, clinical, histological and therapeutic features and classify patients in favourable and unfavourable subsets. Statistical analysis was performed with R software. Survival curves were made with the method of Kaplan-Meier.

Results: We collected 437 patients with a median age of 60 years and a sex-ratio of 1.8. CUP are metastatic to lymph nodes (56.5%), bones (29.7%) and liver (28%). 33% of patients had a unique site of metastases. Adenocarcinoma represented 50.5% of cases while 10.5% are classified in the favourable subgroup. 141 out 437 patients received palliative chemotherapy, 83% of them by cisplatin-based regimens obtaining 13% (58 patients) of objective response. Median survival was 7 months. 24 out 58 patients (41%) relapsed. Poor prognostic factors for survival were: multiple metastases (p=0.00033), >3 sites (p=0.03), undifferentiated carcinoma and adenocarcinoma (p>0.0001), liver metastases (p=0.0137), bone (p=0.00653) and adrenal gland (p=0.0334) metastatic sites. Patients who underwent chemotherapy (p>0.001) and who received cisplat-based regimen had better survival (p=0.01).

Conclusion: Our retrospective study done in the context of a minimal and biological work-up confirmed the difficulty to find the primary in CUP.

K e y - w o r d s

Metastases, carcinoma, unknown primary, survival, prognosis

Carcinomas of unknown primary origin (CUP's) are defined as an histologically confirmed metastatic malignant carcinomas without a detected primary site at the time of therapeutic decision [1]. They account for 0.5-10% of all new diagnosed tumors according to the wok-up extent and is ranked as the 7th-8th malignancy and fourth cause of death by cancer [2]. Failure to locate the primary originates therapeutic problems orienting to a probabilistic approach. CUP remains a very aggressive disease with a poor prognosis and a median survival varying from 5 to 11 months, less than 25% of patients survived more than 1 year [3, 4]. However, a good prognosis subgroup that represents 10 to 20% of CUP's can be identified with specific clinicopathologic subsets and a favorable outcome [5].
In this study, we describe, over a retrospective 13-year study period, incidence, epidemiologic characteristics and the different clinicopathologic subsets of CUP patients treated at the Salah Azaiez Institute.

PATIENTS AND METHODS

We reviewed retrospectively 437 file of histologically-confirmed CUP-patients treated at the SAI from January 1994 to December 2006. We analyzed their epidemiological characteristics, histological findings, immunohistochemistry results for 74 patients (17%), anatomic sites, number of metastases, treatment type, survival and time to progression. Work-up included: Chest X-ray (437), abdominal ultrasound (332), gastroscopy (205), chest computed tomography (184), pelvic ultrasound (175), abdominal computed tomography in 174 cases and seric tumors markers in 153 patients. Median survival was calculated from the time of diagnosis to death.We classified CUP-patients into favourable or unfavourable group according to Pavlidis and Fizazi staging [2]. Statistical analysis was performed with R-software and survival curves calculated with Kaplan-Meier method.

RESULTS

437 CUP-patients were collected at SAI during a 13-year period with an estimated incidence of 34 cases per year. Median and mean ages were 60 and 57 years and there was a male predominance (284M/153F) with a sex-ratio of 1.8. The most common metastatic sites were lymph nodes (56.5%), followed by bones (29.7%) and liver metastases, present in 28% of cases. 295 patients (67%) had multiple and 142 (33%) a single metastastic site (Table 1).
Histologic types were as follows: adenocarcinoma (ADK) in 221 cases (50.5%), well and moderately differenciated adenocarcinomas in 197 cases (45%), undifferentiated carcinoma (UC) in 131 cases (30%), squamous cell carcinoma (SCC) in 61 cases (14%) and neuroendocrine carcinoma (NEC) in 24 cases (5.5%). For the whole population, 166 patients (38%) received best supportive care only (BSCO), 141 (32.3%) underwent chemotherapy (CT) mainly cisplatin-based, 45(13%) surgery and 22 (5%) and 100 (23%) a curative and palliative radiotherapy (RT). Within those that received CT, the number of cycles varied from 1 to 10, done mainly in first line(79%) or more rarely second (15%), 3rd line (4%) or 4th line. After CT, we observed 6% of CR (Complete responses) and 7% of PR(partial responses): 13% (58 patients) of objective response.

Table 1: Patients characteristics

Characteristics		**Number (%)**
Gender	M	284 (64.9)
	F	153 (35.1)
Histologic type	ADK	221 (50.5)
	UC	131 (30)
	SCC	61 (14)
	NEC	24 (5.5)
Site of involvement	Lymph nodes	247 (56.5)
	Bones	130 (29.7)
	Liver	122 (28)
	Lungs	97 (22)
	Pleura	70 (16)
	Peritoneum	46 (10.5)
	Skin	40 (9)
	Brain	36 (8)
	Adrenal gland	20 (4.5)
CUP-type	YM with PDC and ML distribution	3 (0.7)
	F with ADK axill nodes only	1 (0.3)
	SCC inv cervical nodes	18(4)
	NEC	24 (5.5)
	Unfavorable subset	391 (89.5)

M: male; F: female; UD: undifferenciated carcinoma; ADK: adenocarcinoma; SCC: squamous cell carcinoma; NEC: neuroendocrine carcinoma; YM: yang man; PDC: poorly differenciated carcinoma; ML: midline; axill: axillary; inv: involving

We noted 41% (24 /58 cases) of local and/or distant recurrences and a median time to relapse of 4 months (1 to 76). Median overall survival was 7 months (1 to 108). Median survival was 12 months for favourable subsets vs 6 months for unfavourable parameters (p>0.0001). Median survival was better in case of single metastatic site (p=0.00033) and less than 3 metastases (p=0.03) and varied according to the histologic from 7 months for UC and ADK to 8 months for NEC and 11 months for SCC (p>0.0001). Anatomic site influenced median survival being poor in presence of liver MTS (6 ms vs 8 ms, p=0.0137), bone MTS (6.5 vs 8 ms, p=0.00653) or adrenal MTS (6 vs 7 ms, p=0.0334). (Table 2) Median survival was 3 months for patients receiving BSCO vs 10 months if they received CT, better under cisplatin-based regimens (11 vs 9 months, p=0.01).

Table 2: Median Survival according to prognostic factors

Variable		Med Surv	p
Gender			
Male		7	0.08
Female		8	(NS)
Nb of site			
>1		7	0.0003
1		8	
Histological types			
ADK/PDC		7	
NEC		8	> 0.0001
SCC		11	
Metastatic Site			
Liver	yes	6	0.01
	no	8	
Bones	yes	6.5	0.006
	no	8	
Adrenal gland			
	yes	6	0.03
	no	7	
Inguinal lymph node			
	yes	6	0.3
	no	7	(NS)
BSCO			
	yes	4	> 0.0001
	no	9	
CT			
	yes	10	> 0.001
	no	6	

Med sur: median survival; Nb: number ; ADK/PDC : adenocarcinoma/poorly differenciated carcinoma ; NEC : neuroendocrine carcinoma ; SCC : squamous cell carcinoma

DISCUSSION

Within 437 cases of CUP explored in SAI from 1994 to 2006, by a "classic" work-up based on clinical features, imagery, histology and seric tumour markers, primary site(PS) remains unknown in most of our cases. But our important serie represent's the most important African or Arab serie of CUP's arising from a Tunisian National comprehensive cancer center where diagnostic and therapeutic decisions came from multidisciplinary comittees. Other Tunisian data arised from the North Tunisia Cancer Registry which collected from 1994 to 1998 and 1999 to 2003 respectively, 722 cases and 941 cases of CUP's representing during these two periods 4.5% and 3.7% of the all treated cancers [6]. These Tunisian registry data are in accordance with the literature where CUP's rerpresent 3-5% of all cancers [2]. The relative decrease between these two periods for North Tunisia could be attributed to a better and precise work-up using modern imagery (CT-scan, MRI, octreoscan) and also histology/immunohistochemistry with slides review for difficult cases. Median age at CUP diagnosis was, in our study, 60 years with a male predominance in accordance with others series, whereas a female predominance was reported in Shaw and Pimiento studies [2, 7, 8, 9, 10]. Lymph nodes, bones, liver and lungs were the most commun metastatic sites in our study and others series and usually, more than 50% (67% in our study) of CUP-patients had multiple metastastatic sites [3, 11]. In our serie, ADK were predominant compared to SCC or NEC, comparable to others series [3, 4, 7, 12, 13]. Within them favourable subsets represented 10.5% in our serie vs 10 to 20% of CUP in the literature [5]. In CUP's series that are frequently retrospective like our serie, PS identification will leads to a better survival, specially if is breast or ovarian in females, the main objective of the etiologic approach being to identify these good prognostic entities [8, 11, 14, 15, 16, 17]. The National Federation of anticancer centres (FNCLCC) in France proposed guidelines guided by an Evidence-based diagnostic and etiologic work-up based on: medical history, physical examination, chest X-ray, histopathology review with use of immunohistochemistry. If the histologic type is ADK or poorly differenciated carcinoma, mammography and pelvic computed tomography or pelvic ultrasound are indicated in females while PSA, αFP, σHCG have to be prescribed in males.

Others investigations are proposed according to presentation knowing that abdomen/pelvis Ct-scan are more sensitive than ultrasound [17].

In our serie, treatment was based on a probabilistic therapeutic approach according to a multidisciplinary committee and protocol were choosen according to age, sex, general status, co-morbidities, metastatic sites, seric markers and histology/immunohistochemistry. By using mainly cisplatine combinations we reached an objective response rate of 13% and a median survival of 7 months. In literature and retrospective serie comparable to us, CT resulted in 0 to 50% of objective responses and a median survival comprised between 3 and 15 months, without a significant benefit compared to best supportive care only [3,18]. However Platinum or taxanes/ platinum- based regimens have gave higher response rate than previous used regimens and seems to be better than supportive care alone impacting positively on 1 to 3 years survival [13, 19]. Despite these therapeutic modifications, CUP median survival remains around 8-9 months [13, 19]. Randomized trials demonstrated a similar efficacy between platinum combined with gemcitabine or irinotecan vs platin and taxane-based chemotherapy [20-22]. The sole published phase III trial compared paclitaxel/ carboplatin/etoposide and gemcitabine/irinotecan in unfavourable subsets [23]. There were no significant differences between these two arms in terms of median overall survival, median progression free survival and response rate but less toxicities in gemcitabine/irinotecan arm. We find as poorly prognosis parameters, ADK or UC, multiple metastases, > than 3 sites involved, liver, bone, adrenal gland metastases, previously reported by other authors as well

as: performance status >1, supraclavicular nodal metastase, male gender, increased seric alkaline phosphatase [17].

CONCLUSION

Our retrospective and old serie confirms the aggressive behaviour and problems to treat them.

With the use of modern imagery, seric tumor markers and histology/immunohistochemistry, and soon pet-scan in Tunisia, a higher rate of primary site detection could be expected in case of CUP.

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